The catecolamine biosynthetic pathway in DBH deficiency

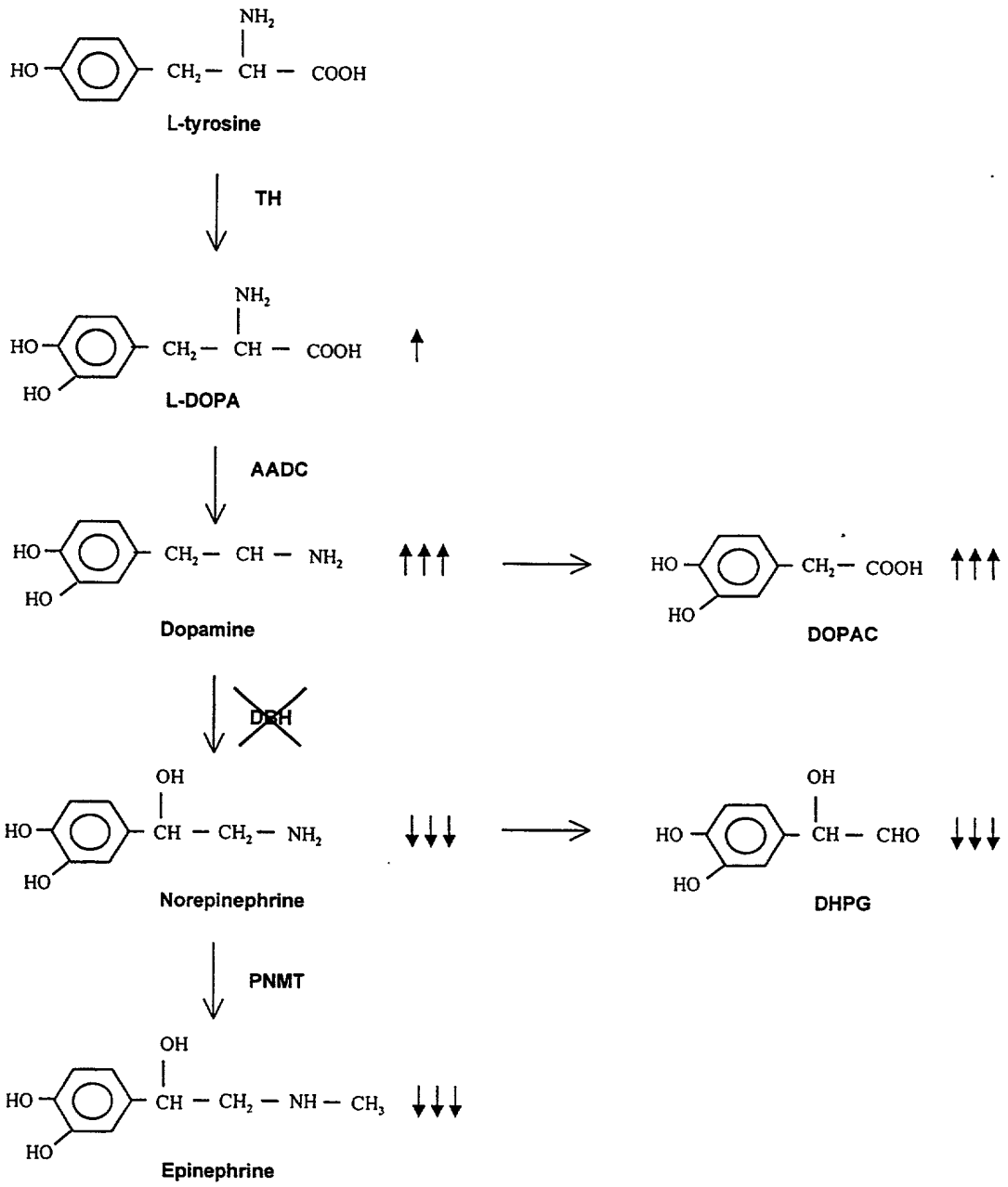


Figure 1

Putative disease-causing mutations in DBH deficiency patient 1

Figure 2 A

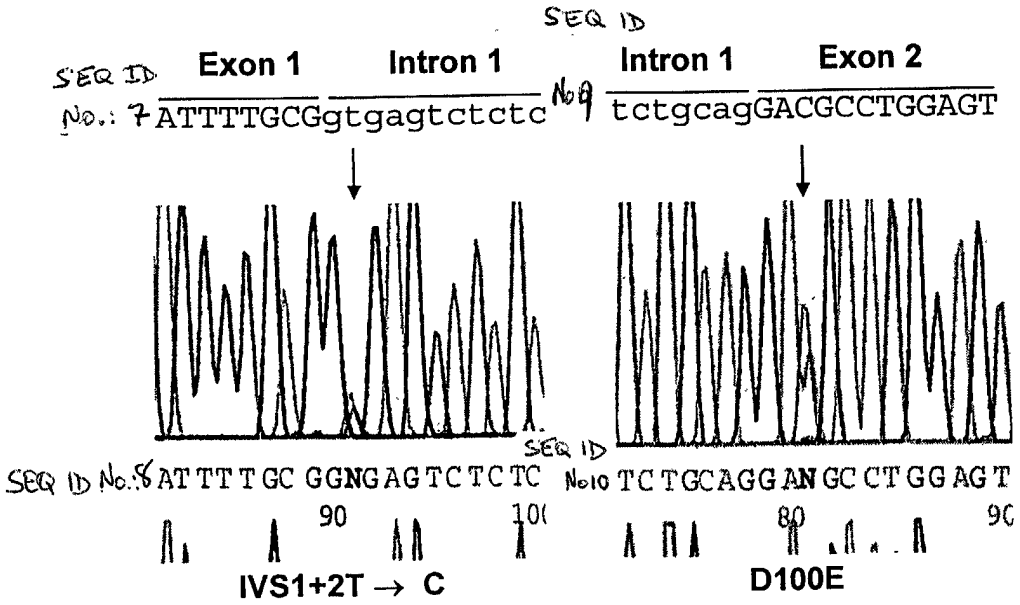
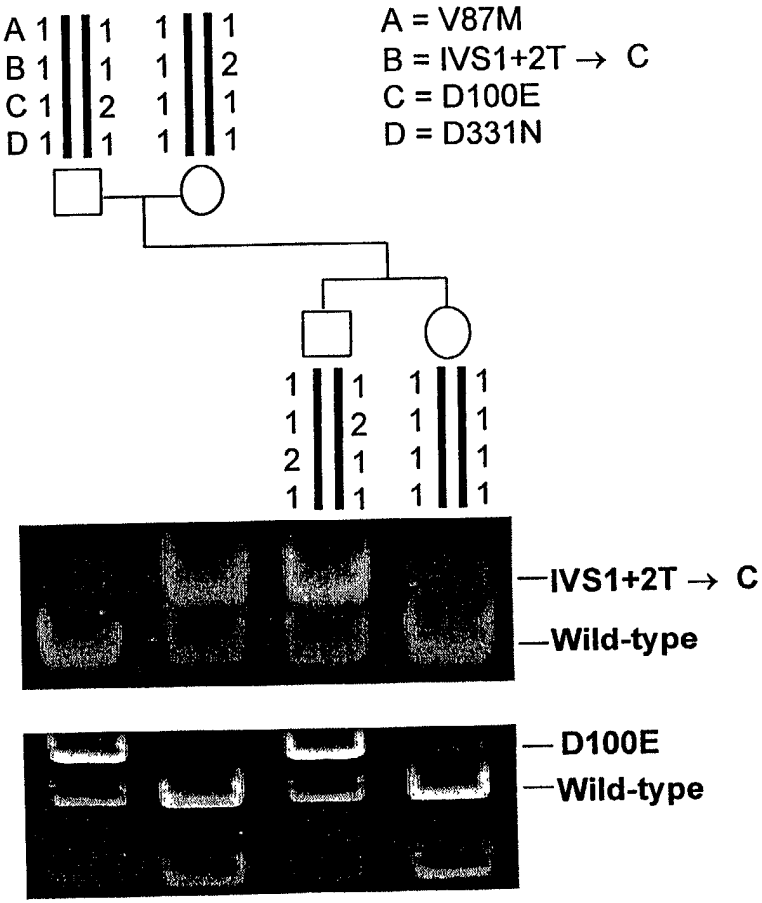


Figure 2 B



Putative disease-causing mutations in DBH deficiency patient 2

Figure 2 C

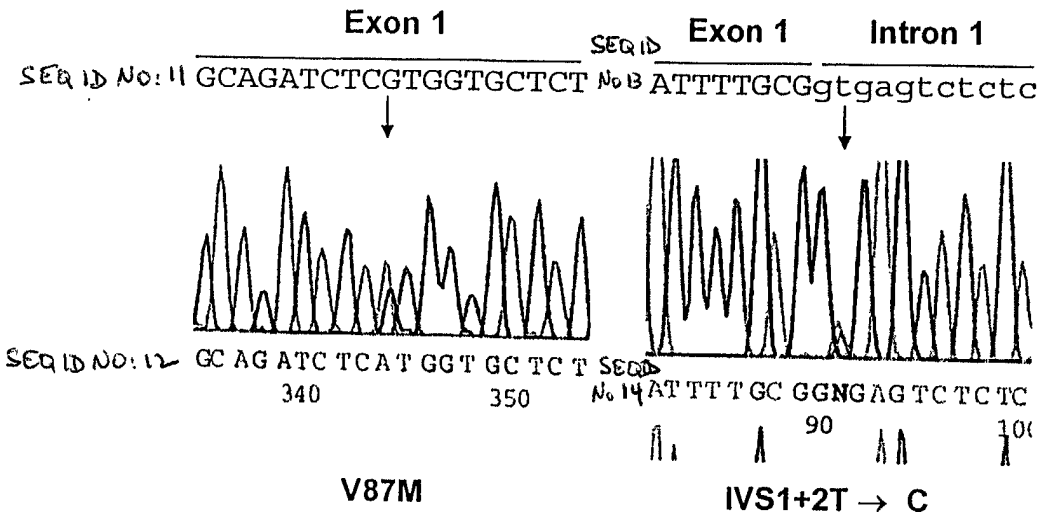


Figure 2 D

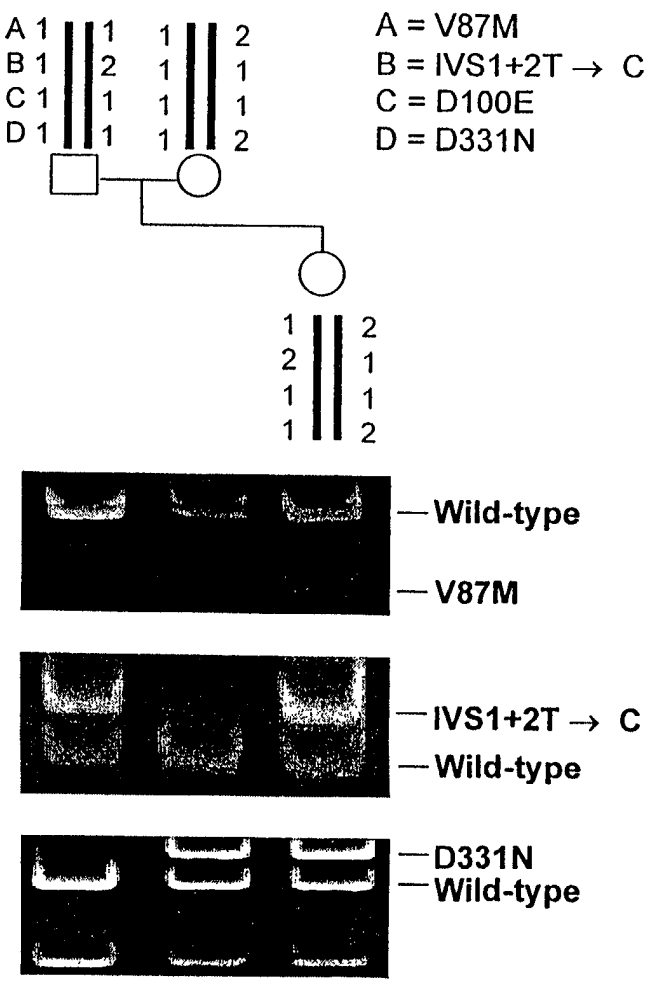


Figure 3 A

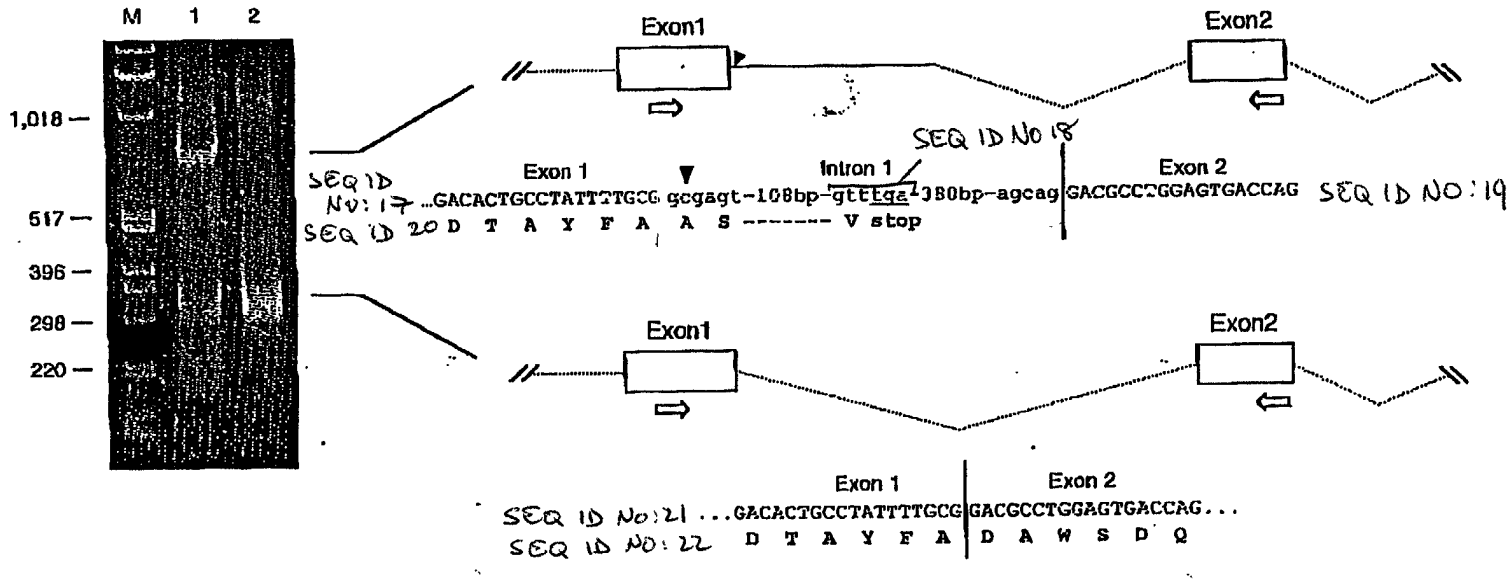


Figure 3 B

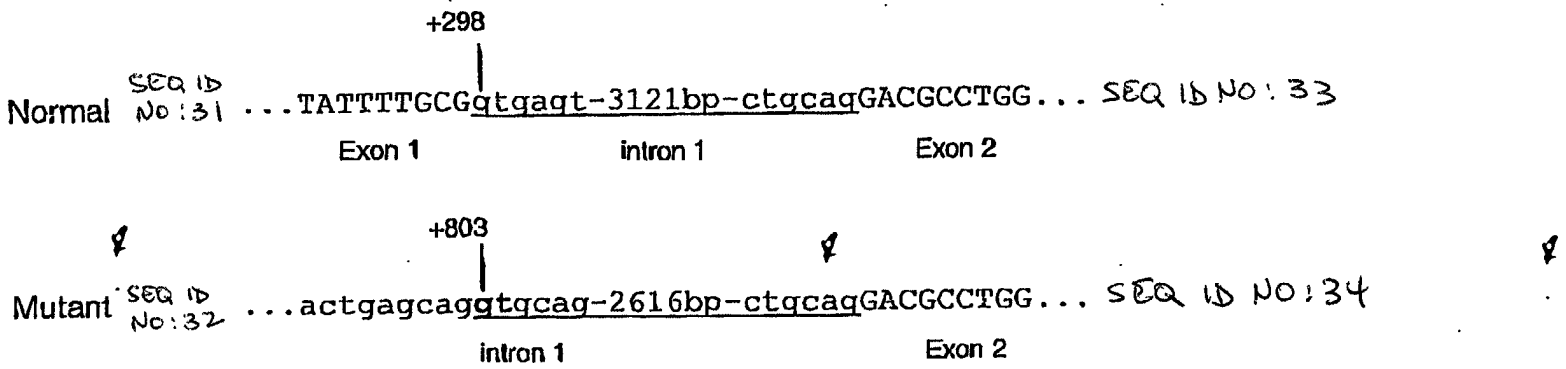
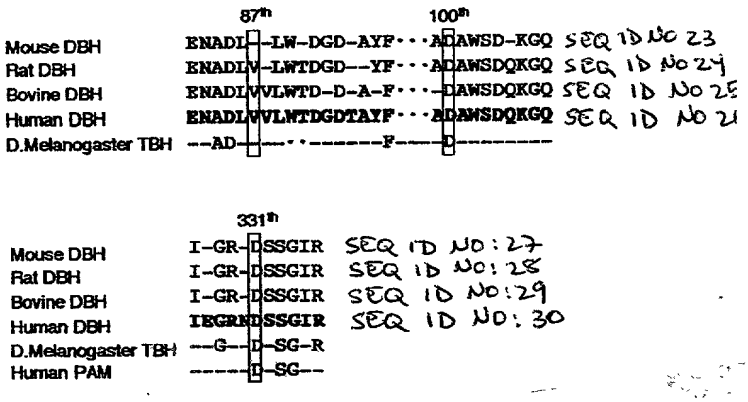


Figure 3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100th
Mouse DBH
Rat DBH
Bovine DBH
Human DBH
D.Melanogaster TBH
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331th
Mouse DBH
Rat DBH
Bovine DBH
Human DBH
D.Melanogaster TBH
Human PAM
I-GR-DSSGIR SEQ ID NO: 27
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IEGRNDSSGIR SEQ ID NO: 30
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-----D-SG--

Figure 4

Table 1. PLASMA LEVELS OF CATECHOLAMINES AND THEIR METABOLITES IN CONTROLS, PATIENTS WITH AUTONOMIC DISORDERS, AND DBH DEFICIENCY.

	Dopa	DA	DOPAC	NE	DHPG	Epinephrine
Normal (n=15)	1,790 ± 150	20 ± 10	2,390 ± 480	252 ± 30	1,290 ± 110	28 ± 15
Pure Autonomic Failure (n=15)	1,300 ± 200	10 ± 10	1,030 ± 280	66 ± 26	627 ± 100	15 ± 8
Multiple System Atrophy (n=23)	1,780 ± 100	20 ± 12	2,300 ± 500	227 ± 27	1,340 ± 90	26 ± 16
DBH Deficiency Patient 1	2,723	172	15,200	<10	<10	<10
DBH Deficiency Patient 2	3,394	141	17,300	<10	<10	<10

In DBH deficiency, precursors of NE (dopa, dopamine) or metabolites (DOPAC) are raised, while products downstream of DBH (NE, epinephrine, DHPG) are absent or at extremely low levels. In contrast, only modest changes in catecholamines and their metabolites are observed in autonomic disorders, such as pure autonomic failure and mutiple system atrophy, which do not directly involve impaired DBH. Units for all data are in pg/ml plasma.

Figure 5

Table 2. SEQUENCE VARIANTS IDENTIFIED IN DBH DEFICIENT PATIENTS.

Location	Variant[a]	Amino acid change	Minor allele frequency[b]
5' flanking	C-1021T	---	0.159
Exon 1	G259A	Val87Met	0
Intron 1	IVS1+2T→C	---	0.011
Exon 2	C300A	Asp100Glu	0
Intron 3	IVS3+8C→T	---	0.017
Exon6	G991A	Asp331Asn	0
Intron 10	IVS10+415A→G	—	0.386

[a]Nucleotide positions are numbered according to the cDNA sequence for exons, or genomic sequence for the 5' flanking region, with the first nucleotide of ATG initiation codon as 1. Positions for introns are according to the genomic sequence starting from the G of the donor site invariant GT.

[b]N=88 unrelated European-Americans

Figure 6

TABLE 3

Clinical features of six reported cases of DBH deficiency

Feature	Frequency (%)
Severe orthostatic hypotension > 40mm Hg	100
Impaired ejaculation*	100
Plasma dopamine >>> plasma norepinephrine	100
Sweating present	100
Sinus arrhythmia present	100
Pressor clonidine response	100
Pressor efficacy of DOPS	100
Ptosis	67
Complicated perinatal course	67
Nocturia	67
Hypoprolactinemia	67
High palate	50
Nasal stuffiness	50
Hypomagnesemia	33
Seizures (with hypotension)	33

* Refers to male patients only (n=2).

Figure 7

DBH Amino Acid Sequence

```
Met Arg Glu Ala Ala Phe Met Tyr Ser Thr Ala Val Ala Ile Phe Leu
 1               5                  10                  15
Val Ile Leu Val Ala Ala Leu Gln Gly Ser Ala Pro Arg Glu Ser Pro
            20                  25                  30
Leu Pro Tyr His Ile Pro Leu Asp Pro Glu Gly Ser Leu Glu Leu Ser
        35                  40                  45
Trp Asn Val Ser Tyr Thr Gln Glu Ala Ile His Phe Gln Leu Leu Val
    50                  55                  60
Arg Arg Leu Lys Ala Gly Val Leu Phe Gly Met Ser Asp Arg Gly Glu
65                  70                  75                  80
Leu Glu Asn Ala Asp Leu Val Val Leu Trp Thr Asp Gly Asp Thr Ala
                85                  90                  95
Tyr Phe Ala Asp Ala Trp Ser Asp Gln Lys Gly Gln Ile His Leu Asp
            100                 105                 110
Pro Gln Gln Asp Tyr Gln Leu Leu Gln Val Gln Arg Thr Pro Glu Gly
        115                 120                 125
Leu Thr Leu Leu Phe Lys Arg Pro Phe Gly Thr Cys Asp Pro Lys Asp
    130                 135                 140
Tyr Leu Ile Glu Asp Gly Thr Val His Leu Val Tyr Gly Ile Leu Glu
145                 150                 155                 160
Glu Pro Phe Arg Ser Leu Glu Ala Ile Asn Gly Ser Gly Leu Gln Met
                165                 170                 175
Gly Leu Gln Arg Val Gln Leu Leu Lys Pro Asn Ile Pro Glu Pro Glu
            180                 185                 190
Leu Pro Ser Asp Ala Cys Thr Met Glu Val Gln Ala Pro Asn Ile Gln
        195                 200                 205
Ile Pro Ser Gln Glu Thr Thr Tyr Trp Cys Tyr Ile Lys Glu Leu Pro
    210                 215                 220
Lys Gly Phe Ser Arg His His Ile Ile Lys Tyr Glu Pro Ile Val Thr
225                 230                 235                 240
Lys Gly Asn Glu Ala Leu Val His His Met Glu Val Phe Gln Cys Ala
                245                 250                 255
Pro Glu Met Asp Ser Val Pro His Phe Ser Gly Pro Cys Asp Ser Lys
            260                 265                 270
Met Lys Pro Asp Arg Leu Asn Tyr Cys Arg His Val Leu Ala Ala Trp
        275                 280                 285
Ala Leu Gly Ala Lys Ala Phe Tyr Tyr Pro Glu Glu Ala Gly Leu Ala
    290                 295                 300
Phe Gly Gly Pro Gly Ser Ser Arg Tyr Leu Arg Leu Glu Val His Tyr
305                 310                 315                 320
His Asn Pro Leu Val Ile Glu Gly Arg Asn Asp Ser Ser Gly Ile Arg
                325                 330                 335
Leu Tyr Tyr Thr Ala Lys Leu Arg Arg Phe Asn Ala Gly Ile Met Glu
            340                 345                 350
Leu Gly Leu Val Tyr Thr Pro Val Met Ala Ile Pro Pro Arg Glu Thr
        355                 360                 365
Ala Phe Ile Leu Thr Gly Tyr Cys Thr Asp Lys Cys Thr Gln Leu Ala
    370                 375                 380
Leu Pro Pro Ser Gly Ile His Ile Phe Ala Ser Gln Leu His Thr His
385                 390                 395                 400
Leu Thr Gly Arg Lys Val Val Thr Val Leu Val Arg Asp Gly Arg Glu
                405                 410                 415
Trp Glu Ile Val Asn Gln Asp Asn His Tyr Ser Pro His Phe Gln Glu
            420                 425                 430
```

Figure 8

```
Ile Arg Met Leu Lys Lys Val Val Ser Val His Pro Gly Asp Val Leu
        435                 440                 445
Ile Thr Ser Cys Thr Tyr Asn Thr Glu Asp Arg Glu Leu Ala Thr Val
    450                 455                 460
Gly Gly Phe Gly Ile Leu Glu Glu Met Cys Val Asn Tyr Val His Tyr
465                 470                 475                 480
Tyr Pro Gln Thr Gln Leu Glu Leu Cys Lys Ser Ala Val Asp Ala Gly
                485                 490                 495
Phe Leu Gln Lys Tyr Phe His Leu Ile Asn Arg Phe Asn Asn Glu Asp
            500                 505                 510
Val Cys Thr Cys Pro Gln Ala Ser Val Ser Gln Gln Phe Thr Ser Val
        515                 520                 525
Pro Trp Asn Ser Phe Asn Arg Asp Val Leu Lys Ala Leu Tyr Ser Phe
    530                 535                 540
Ala Pro Ile Ser Met His Cys Asn Lys Ser Ser Ala Val Arg Phe Gln
545                 550                 555                 560
Gly Glu Trp Asn Leu Gln Pro Leu Pro Lys Val Ile Ser Thr Leu Glu
                565                 570                 575
Glu Pro Thr Pro Gln Cys Pro Thr Ser Gln Gly Arg Ser Pro Ala Gly
            580                 585                 590
Pro Thr Val Val Ser Ile Gly Gly Gly Lys Gly
        595                 600
```


Figure 8 (continued)

DBH cDNA

```
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Figure 9

DBH Genomic Sequence

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Figure 10

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Figure 10 (continued)

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Figure 10 (continued)

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Figure 10 (continued)

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Figure 10 (continued)

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Figure 10 (continued)

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Figure 10 (continued)

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Figure 10 (continued)

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Figure 10 (continued)

SEQ ID NO:	Amino Acid at position 87
38	ENADL**X**VLWTD
39	DRGELENADL**X**VLWTDGDTAY
40	LFGMSDRGELENADL**X**VLWTDGDTAYFADAW
41	LKAGVLFGMSDRGELENADL**X**VLWTDGDTAYFADAWSDQKG

X indicates amino acid position 87. X may be valine, methionine, or a conservative substition for either valine or methionine. X may also be absent.

SEQ ID NO:	Amino acid position 100
42	DTAYFA**X**AWSDQ
43	WTDGDTAYFA**X**AWSDQKGQIH
44	DLVVLWTDGDTAYFA**X**AWSDQKGQIHLDPQQ
45	ELENADLVVLWTDGDTAYFA**X**AWSDQKGQIHLDPQQDYQLL

X indicates amino acid position 100. **X** may be aspartic acid, glutamic acid, or a conservative substitution for those amino acids. **X** may also be absent.

SEQ ID NO:	Amino acid position 331
46	IEGRN**X**SSGIR
47	HNPLVIEGRN**X**SSGIRLYYTA
48	LEVHYHNPLVIEGRN**X**SSGIRLYYTAKLRRF
49	SRYLRLEVHYHNPLVIEGRN**X**SSGIRLYYTAKLRRFNAGIM

X indicates amino acid position 331. **X** may be aspartic acid, glutamic acid, or a conservative substitution for those amino acids. **X** may also be absent.

Figure 11